

Day : Thursday  
Date: 6/8/2006  
Time: 22:45:18

PALM INTRANET

# Inventor Information for 09/424519

Inventor Name	City	State/Country
MITCHELL, JAMES B.	DAMASCUS	MARYLAND
RUSSO, ANGELO	BETHESDA	MARYLAND
CHERUKURI, MURALI KRISHNA	ROCKVILLE	MARYLAND
DELUCA, ANNE MARIE	TUCSON	ARIZONA

[Appln Info](#)[Contents](#)[Petition Info](#)[Atty/Agent Info](#)[Continuity Data](#)[Foreign Data](#)[Inventors](#)

Search Another: Application#   or Patent#

PCT /  /   or PG PUBS #

Attorney Docket #

Bar Code #

To go back use Back button on your browser toolbar.

Back to [PALM](#) | [ASSIGNMENT](#) | [OASIS](#) | [Home page](#)

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	766	514/315.ccls.	USPAT	OR	OFF	2006/06/08 22:25
L2	9	l1 and tempol	USPAT	OR	OFF	2006/06/08 22:25
L3	567	514/330.ccls.	USPAT	OR	OFF	2006/06/08 22:42
L4	0	l3 and tempol	USPAT	OR	OFF	2006/06/08 22:25
L5	1	l3 and nitroxide	USPAT	OR	OFF	2006/06/08 22:32
L6	683	514/345.ccls.	USPAT	OR	OFF	2006/06/08 22:43
L7	571	514/376.ccls.	USPAT	OR	OFF	2006/06/08 22:43
L8	2484	l1 or l3 or l6 or l7	USPAT	OR	OFF	2006/06/08 22:43
L9	9	l8 and tempol	USPAT	OR	OFF	2006/06/08 22:43

(FILE 'HOME' ENTERED AT 10:17:33 ON 08 JUN 2006)

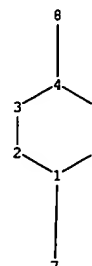
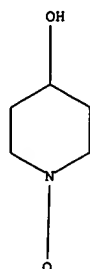
FILE 'REGISTRY' ENTERED AT 10:17:39 ON 08 JUN 2006

L1 STRUCTURE UPLOADED  
L2 0 S SSS L1 FULL  
L3 0 S SSS L1 FULL  
L4 STRUCTURE UPLOADED  
L5 692 S SSS FULL L4

FILE 'CAPLUS, EMBASE, BIOSIS, WPIX' ENTERED AT 10:19:41 ON 08 JUN 2006

L6 4074 S L5  
L7 4263314 S TUMOR OR TUMOUR OR CANCER OR NEOPLASTIC? OR NEOPLAS? OR LEUKE  
L8 118937 S P53  
L9 14 S L6 AND L8  
L10 283 S L6 AND L7  
L11 8 DUP REM L9 (6 DUPLICATES REMOVED)  
L12 8 FOCUS L11 1-  
L13 206 DUP REM L10 (77 DUPLICATES REMOVED)  
L14 206 FOCUS L13 1-  
L15 3 S L14 AND (FRAUMENI OR ATAXIA)

=>



chain nodes :

7 8

ring nodes :

1 2 3 4 5 6

chain bonds :

1-7 4-8

ring bonds :

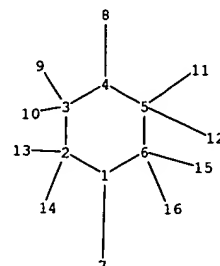
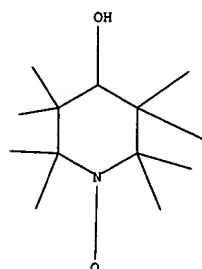
1-2 1-6 2-3 3-4 4-5 5-6

exact/norm bonds :

1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS8:CLASS



chain nodes :

7 8 9 10 11 12 13 14 15 16

ring nodes :

1 2 3 4 5 6

chain bonds :

1-7 2-13 2-14 3-9 3-10 4-8 5-11 5-12 6-15 6-16

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6

exact/norm bonds :

1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6

exact bonds :

2-13 2-14 3-9 3-10 5-11 5-12 6-15 6-16

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS8:CLASS9:CLASS  
10:CLASS11:CLASS12:CLASS13:CLASS14:CLASS15:CLASS16:CLASS

ACCESSION NUMBER: 2005:480296 CAPLUS

DOCUMENT NUMBER: 143:166161

TITLE: Cancer chemoprevention by the antioxidant tempol acts partially via the p53 tumor suppressor

AUTHOR(S): Erker, Laura; Schubert, Ralf; Yakushiji, Hiroyuki; Barlow, Carrolee; Larson, Denise; Mitchell, James B.; Wynshaw-Boris, Anthony

CORPORATE SOURCE: Department of Pediatrics, UCSD School of Medicine, La Jolla, CA, 92093, USA

SOURCE: Human Molecular Genetics (2005), 14(12), 1699-1708  
CODEN: HMGE5; ISSN: 0964-6906

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We previously demonstrated that the nitroxide antioxidant tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) increased latency to tumorigenesis and doubled (100%) the lifespan of Atm-deficient mice, a mouse model of ataxia telangiectasia, which displays accelerated oxidative damage and stress. Tempol treatment of cancer-prone p53-deficient mice resulted in a small but significant (25%) increase in lifespan by prolonging latency to tumorigenesis, demonstrating that existing oxidative stress and damage are not necessary for the chemopreventive effects of tempol. However, the relatively small effect on latency in p53-deficient mice and the finding that tempol-mediated resistance to oxidative insult was p53-dependent suggested a more direct role of p53 in the chemopreventive effects of tempol. Surprisingly, tempol treatment specifically increased serine 18 phosphorylation of p53 (but not  $\gamma$ -H2AX) and p21 expression in primary thymocytes in vitro in a p53-dependent fashion. Inhibition of phosphoinositide 3-kinase (PI3K) family members suggested that SMG-1 was responsible for the tempol-mediated enhancement of p53 serine 18 phosphorylation. These data suggest that the chemopreventive effect of tempol is not solely due to the reduction of oxidative stress and damage but may also be related to redox-mediated signaling functions that include p53 pathway activation.

IT Ionizing radiation

(DNA damage; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT DNA damage

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(DSB reduction by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Antitumor agents

Signal transduction, biological

Transformation, neoplastic

(cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT p53 (protein)

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Neoplasm

(chemoprevention; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Body weight

(not reduced by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(p21, induction by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Metabolic pathways

(p53 pathway activation by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Mus musculus

(p53-deficient; cancer chemoprevention by the antioxidant tempol acts partially via the p53)

IT Phosphorylation, biological

(protein; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT . Oxidative stress, biological  
(reduction; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT Thymus gland  
(thymocyte; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT 56-45-1, Serine, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(18 **p53** phosphorylation of; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT 182970-53-2, Protein kinase Atm 402936-89-4, SMG-1 protein kinase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT 2226-96-2, Tempol  
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)

IT 115926-52-8, Phosphoinositide 3-kinase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibition of phosphoinositide 3-kinase (PI3K) family members suggested that SMG-1 was responsible for the tempol-mediated enhancement of **p53** serine 18 phosphorylation)

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 8 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005059453 EMBASE  
TITLE: Role of the **p53**/p21 system in the response of human colon carcinoma cells to doxorubicin.  
AUTHOR: Ravizza R.; Gariboldi M.B.; Passarelli L.; Monti E.  
CORPORATE SOURCE: E. Monti, Dept. of Struct./Functional Biology, Section of Pharmacology, University of Insubria, Via A. da Giussano 10, 21052 Busto Arsizio VA, Italy.  
elena.monti@uninsubria.it  
SOURCE: BMC Cancer, (15 Dec 2004) Vol. 4, pp. 10p. .  
Refs: 43  
ISSN: 1471-2407 CODEN: BCMACL  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 016 Cancer  
026 Immunology, Serology and Transplantation  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index  
048 Gastroenterology  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 18 Feb 2005  
Last Updated on STN: 18 Feb 2005

AB Background: Colon adenocarcinomas are refractory to a number of widely used anticancer agents. Multifactorial mechanisms have been implicated in this intrinsically resistant phenotype, including deregulation of cell death pathways. In this regard, the **p53** protein has a well established role in the control of tumor cell response to DNA damaging agents; however, the relationship between **p53**-driven genes and drug sensitivity remains controversial. The present study investigates the role of the **p53**/p21 system in the response of human colon carcinoma cells to treatment with the cytotoxic agent doxorubicin (DOX) and the possibility to modify the therapeutic index of DOX by modulation of **p53** and/or p21 protein levels. Methods: The relationship between **p53** and p21 protein levels and the cytotoxic effect of DOX was investigated, by MTT assay and western blot analysis, in HCT116 (**p53**-positive) and HT29 (**p53**-negative) colon cancer

cells. We then assessed the effects of DOX in two isogenic cell lines derived from HCT116 by abrogating the expression and/or function of p53 and p21 (HCT116-E6 and HCT116 p21-/-, respectively). Finally, we evaluated the effect of pre-treatment with the piperidine nitroxide Tempol (TPL), an agent that was reported to induce p21 expression irrespective of p53 status, on the cytotoxicity of DOX in the four cell lines. Comparisons of IC50 values and apoptotic cell percentages were performed by ANOVA and Bonferroni's test for independent samples. C.I. calculations were performed by the combination Index method. Results: Our results indicate that, in the colon carcinoma cell lines tested, sensitivity to DOX is associated with p21 upregulation upon drug exposure, and DOX cytotoxicity is potentiated by pretreatment with TPL, but only in those cell lines in which p21 can be upregulated. Conclusions: p21 induction may significantly contribute to the response of colon adenocarcinomas cells to DOX treatment; and small molecules that can exploit p53-independent pathways for p21 induction, such as TPL, may find a place in chemotherapeutic protocols for the clinical management of colorectal cancer, where p53 function is often lost, due to genetic or epigenetic defects or to post-transcriptional inactivating mechanisms. .COPYRGT. 2004 Ravizza et al; licensee BioMed Central Ltd.

L12 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:831323 CAPLUS

DOCUMENT NUMBER: 142:34547

TITLE: The effects of antioxidants on radiation-induced apoptosis pathways in TK6 cells

AUTHOR(S): Samuni, Ayelet M.; DeGraff, William; Cook, John A.; Krishna, Murali C.; Russo, Angelo; Mitchell, James B.

CORPORATE SOURCE: Radiation Biology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Free Radical Biology & Medicine (2004), 37(10), 1648-1655

CODEN: FRBMEH; ISSN: 0891-5849

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study was designed to determine if radiation-mediated activation of the apoptotic pathways would be influenced by antioxidants and if a correlation would be found between radioprotection and changes in transduction pathways. Human lymphoblastoid TK6 cells, known to undergo apoptosis as a result of radiation, were irradiated (6 Gy) with and without antioxidants, and then whole-cell lysates were collected. Parallel studies were conducted to assess the survival (clonogenic assay) and apoptotic index. The impacts of two nitroxide antioxidants, tempol and CAT-1, differing in cell permeability, as well as the sulfhydryl antioxidant N-acetyl-L-cysteine (L-NAC), were estimated. Changes in apoptotic pathway proteins and p53 were assessed by Western blotting. Fraction of apoptotic cells was determined by flow cytometry. Tempol (10 mM), which readily enters cells, partially radioprotected TK6 cells against clonogenic killing, but had no effect on radiation-induced apoptotic parameters such as cleaved caspase 3 or cleaved PARP. Tempol alone did not induce cytotoxicity, yet did increase cleaved PARP levels. The radiation-induced increase in p53 protein was partly inhibited by tempol, but was unaffected by CAT-1 and L-NAC. Both CAT-1 (10 mM), which does not enter cells, and L-NAC (10 mM) had no radioprotective effect on cell survival. Although L-NAC did not protect against radiation-induced cytotoxicity, it completely inhibited radiation-induced increase in cleaved caspase 3 and cleaved PARP. Collectively, the results question the validity of using selected apoptosis pathway members as sole indicators of cytotoxicity.

IT Antioxidants

Apoptosis

Human

Ionizing radiation

Lymphoblast

Radioprotectants

Transduction, genetic

(antioxidants effect on radiation-induced apoptosis)



IT **p53** (protein)  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antioxidants effect on radiation-induced apoptosis)

IT 9055-67-8, Poly(ADP-ribose) polymerase 169592-56-7, Caspase 3  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (antioxidants effect on radiation-induced apoptosis)

IT 616-91-1, N-Acetyl-L-cysteine 2226-96-2, Tempol 64486-64-2,  
 CAT-1  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (antioxidants effect on radiation-induced apoptosis)

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:720111 CAPLUS  
 DOCUMENT NUMBER: 134:36766  
 TITLE: The nitroxide Tempol induces oxidative stress,  
 p21WAF1/CIP1, and cell death in HL60 cells  
 AUTHOR(S): Gariboldi, M. B.; Rimoldi, V.; Supino, R.; Favini, E.;  
 Monti, E.  
 CORPORATE SOURCE: Section of Pharmacology, Department of Structural and  
 Functional Biology, University of Insubria, Varese,  
 Milan, Italy  
 SOURCE: Free Radical Biology & Medicine (2000), 29(7), 633-641  
 CODEN: FRBMEH; ISSN: 0891-5849  
 PUBLISHER: Elsevier Science Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The antiproliferative effect of Tempol, a stable nitroxide free radical,  
 was investigated on the **p53**-neg. human leukemia cell line HL60.  
 A concentration- and time-dependent inhibition of cell growth was observed that  
 appears to be due to induction of apoptosis. Involvement of oxidative  
 stress is indicated by a concentration-dependent increase in intracellular  
 peroxides and a parallel decrease in total cellular glutathione; in addition,  
 increased survival rates were observed in cells simultaneously treated with  
 Tempol and the antioxidant N-acetylcysteine. Tempol did not affect the  
 relative levels of Bax and Bcl2, whereas p21WAF1/CIP1 was enhanced in a  
 concentration- and time-dependent fashion; this effect was partially inhibited by  
 N-acetylcysteine, was maintained for up to 8 h after Tempol removal, and  
 seemed to depend on continuing protein synthesis. The increase in  
 p21WAF1/CIP1 was accompanied by a parallel accumulation of cells in the G1  
 phase of the cycle and by a decrease in the 110 kDa form of pRb. Our  
 results suggest that **p53**-independent induction of p21WAF1/CIP1  
 mediates the antiproliferative effect of Tempol; on the basis of this  
 observation, the nitroxide could be proposed as an useful adjunct to the  
 treatment of **p53**-deficient tumors, which are often refractory to  
 standard chemotherapy.

IT Interphase (cell cycle)  
 (G1-phase; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and  
 cell death in HL60 cells)

IT Animal cell line  
 (HL-60; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and  
 cell death in HL60 cells)

IT Transcription factors  
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
 BIOL (Biological study); OCCU (Occurrence)  
 (Rb, 110,00-mol.-weight; nitroxide Tempol induces oxidative stress,  
 p21WAF1/CIP1, decreased pRb levels and cell death in HL60 cells)

IT Antitumor agents  
 (leukemia; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and  
 cell death in HL60 cells)

IT Peroxides, biological studies  
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
 BIOL (Biological study); OCCU (Occurrence)  
 (lipid; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and  
 cell death in HL60 cells)

IT Apoptosis

Oxidative stress, biological  
Proliferation inhibition  
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT Translation, genetic  
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells dependent on)

IT Cyclin dependent kinase inhibitors  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
BIOL (Biological study); OCCU (Occurrence)  
(p21CIP1/WAF1; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT Lipids, biological studies  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
BIOL (Biological study); OCCU (Occurrence)  
(peroxides; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT 70-18-8, Glutathione, biological studies  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
BIOL (Biological study); OCCU (Occurrence)  
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT **2226-96-2, Tempol**  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:14804 CAPLUS

DOCUMENT NUMBER: 142:254009

TITLE: The piperidine nitroxide Tempol potentiates the cytotoxic effects of temozolomide in human glioblastoma cells

AUTHOR(S): Ravizza, Raffaella; Cereda, Elena; Monti, Elena; Gariboldi, Marzia B.

CORPORATE SOURCE: Department of Structural and Functional Biology, Section of Pharmacology, University of Insubria, Busto Arsizio, I-21052, Italy

SOURCE: International Journal of Oncology (2004), 25(6), 1817-1822

CODEN: IJONES; ISSN: 1019-6439

PUBLISHER: International Journal of Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Temozolomide (TMZ) is a methylating agent with promising antitumor efficacy for the treatment of melanomas and intermediate-grade gliomas. Unfortunately, its use in the management of high-grade gliomas (glioblastomas) is limited by multifaceted resistance mechanisms. The aim of this study was to evaluate the possibility to improve the cytotoxic response of two human glioblastoma cell lines, U87MG and U373MG, to TMZ by the use of Tempol (TPL), a low mol. weight piperidine nitroxide that has been shown to inhibit in vitro and in vivo growth of murine glioma cells. To this purpose, we used two different schedules for the combined exposure to the two agents. Our data indicate that TPL synergizes with TMZ in both U87MG and U373MG cells for both schedules tested. This effect is accompanied by an increase in apoptotic cell death and by changes in the expression of genes involved in control of the apoptotic process. TPL was also observed to induce a cell-type specific decrease in GSH levels and in GSH-related enzyme activities that could contribute to its sensitizing effect.

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bax; exposure to TMZ had no effect on Bax level in human glioblastoma cell lines U87MG and U373MG whereas TPL caused dose-dependent increase in protein level in U373MG cell line while no effect was seen in U87MG cell line)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bcl-2; Bcl-2 level was unchanged following exposure to temozolomide and tempol in human glioblastoma cell lines U87MG and U373MG)

IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(Bcl-xL; exposure to TPL had no effect on Bcl-XL level in human glioblastoma cell lines U87MG and U373MG whereas TMZ caused dose-dependent increase in protein level in U87MG cell line while no effect was seen in U373MG cell line)

IT Methylation  
(agents; methylating agent temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT Antitumor agents  
(anticancer agent temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT Neuroglia, neoplasm  
(glioblastoma; temozolomide cytotoxicity increased dose-dependently by tempol treatment, increased apoptosis was seen in human glioblastoma cell lines U87MG and U373MG)

IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(p21; exposure to tempol and high dose TMZ caused dose-dependent increase in p21 level in human glioblastoma cell line U373MG while no effect was seen in U87MG cell line)

IT **p53** (protein)  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**p53** level was unchanged following exposure to temozolomide and tempol in human glioblastoma cell lines U87MG and U373MG)

IT Drug interactions  
(synergistic; temozolomide cytotoxicity increased dose-dependently by tempol treatment exhibiting synergistic effect in human glioblastoma cell lines U87MG and U373MG)

IT Human  
(temozolomide cytotoxicity increased dose-dependently by tempol treatment, increased apoptosis was seen in human glioblastoma cell lines U87MG and U373MG)

IT Apoptosis  
(temozolomide treatment in combination with tempol induced dose-dependent increase in apoptosis more than monotherapy in human glioblastoma cell lines U87MG and U373MG)

IT 70-18-8, Glutathione, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(exposure to tempol caused significant decrease in GSH level in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 9001-48-3, Glutathione reductase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(exposure to tempol caused significant decrease in GSR level in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 50812-37-8, Glutathione transferase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(exposure to tempol caused significant decrease in GST activity in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 85622-93-1, Temozolomide  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT **2226-96-2**, Tempol  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(tempol treatment increased cytotoxicity of temozolomide dose-dependently in human glioblastoma cell lines U87MG and U373MG)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 8 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003115021 EMBASE  
TITLE: Study of in vitro and in vivo effects of the piperidine nitroxide Tempol - A potential new therapeutic agent for gliomas.  
AUTHOR: Gariboldi M.B.; Ravizza R.; Petterino C.; Castagnaro M.; Finocchiaro G.; Monti E.  
CORPORATE SOURCE: E. Monti, DBSF, Laboratory of Pharmacology, University of Insubria, Via A. da Giussano, 12, 21052 Busto Arsizio (VA), Italy. elena.monti@uninsubria.it  
SOURCE: European Journal of Cancer, (2003) Vol. 39, No. 6, pp. 829-837. .  
Refs: 28  
ISSN: 0959-8049 CODEN: EJCAEL  
PUBLISHER IDENT.: S 0959-8049(02)00742-6  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 008 Neurology and Neurosurgery  
016 Cancer  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 27 Mar 2003  
Last Updated on STN: 27 Mar 2003

AB The identification of novel therapeutic agents for the management of malignant gliomas represents an area of active research. Here, we show that Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl; TPL), a stable nitroxide free radical, inhibits the growth of C6 glioma cells both in vitro and in vivo. Morphological features of apoptosis were apparent in C6 cells following in vitro treatment with TPL. Cell death was preceded by dose-dependent increase in p21(WAF1/CIP1) expression, without apparent stabilisation of the TP53 gene product. When C6 cells were grown as xenografts in nude mice, treatment with TPL induced a significant dose-dependent decrease in tumour growth, without signs of general or organ toxicity. Tumours from treated mice showed an increase in the number of apoptotic cells and a decrease in the rate of neo-vascularisation compared with tumours from control mice. Our findings suggest a potential use for TPL as a novel antiproliferative agent for the treatment of malignant gliomas. .COPYRGHT. 2003 Elsevier Science Ltd. All rights reserved.

L12 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
ACCESSION NUMBER: 2003:441858 BIOSIS  
DOCUMENT NUMBER: PREV200300441858  
TITLE: Effects of p21waf1/cip1 expression in the response of human colon cancer cells to doxorubicin.  
AUTHOR(S): Monti, Elena [Reprint Author]; Ravizza, Raffaella [Reprint Author]; Cereda, Elena [Reprint Author]; Gariboldi, Marzia B. [Reprint Author]  
CORPORATE SOURCE: DBSF, University of Insubria, Busto Arsizio, VA, Italy  
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 132. print.  
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.  
ISSN: 0197-016X.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 24 Sep 2003  
Last Updated on STN: 24 Sep 2003

IT Major Concepts  
Digestive System (Ingestion and Assimilation); Pharmacology; Tumor Biology  
IT Diseases  
colon cancer: digestive system disease, neoplastic disease  
Colonic Neoplasms (MeSH)

IT Chemicals & Biochemicals  
doxorubicin: antineoplastic-drug, efficacy; p21: expression;  
p21-waf1/cip1: expression; p53: expression; tempol

ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
HCT116 cell line (cell line): human colon cancer cells  
HT29 cell line (cell line): human colon cancer cells  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
RN 23214-92-8 (doxorubicin)  
2226-96-2 (tempol)

L12 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN  
ACCESSION NUMBER: 2001:369567 BIOSIS  
DOCUMENT NUMBER: PREV200100369567  
TITLE: Synergistic antiproliferative effects of the piperidine  
nitroxide Tempol and Temozolomide against human glioma cell  
lines.  
AUTHOR(S): Gariboldi, Marzia B. [Reprint author]; Ravizza, Raffaella  
[Reprint author]; Rimoldi, Valeria [Reprint author]; Monti,  
Elena [Reprint author]  
CORPORATE SOURCE: University of Insubria, Milan, Italy  
SOURCE: Proceedings of the American Association for Cancer Research  
Annual Meeting, (March, 2001) Vol. 42, pp. 84-85. print.  
Meeting Info.: 92nd Annual Meeting of the American  
Association for Cancer Research. New Orleans, LA, USA.  
March 24-28, 2001. American Association for Cancer  
Research.  
ISSN: 0197-016X.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 2 Aug 2001  
Last Updated on STN: 19 Feb 2002

IT Major Concepts  
Pharmacology; Tumor Biology  
IT Diseases  
malignant glioma: neoplastic disease  
Glioma (MeSH)  
IT Chemicals & Biochemicals  
GSH [glutathione]; Temozolamide: antineoplastic-drug, piperidine  
nitroxide, synergistic effects; Tempol: antineoplastic-drug, piperidine  
nitroxide, synergistic effects; cip1; p53; waf1

IT Miscellaneous Descriptors  
Meeting Abstract  
ORGN Classifier  
Hominidae 86215  
Super Taxa  
Primates; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
U373 cell line: human glioma cells  
U87 cell line: human glioma cells  
Taxa Notes  
Animals, Chordates, Humans, Mammals, Primates, Vertebrates  
ORGN Classifier  
Muridae 86375  
Super Taxa  
Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
Organism Name  
C6 cell line: mouse glioma cells  
Taxa Notes  
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
Rodents, Vertebrates  
RN 70-18-8 (GSH)  
70-18-8 (glutathione)  
2226-96-2 (Tempol)

This is Google's cache of <http://www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html> as retrieved on Jun 5, 2006 15:05:26 GMT.

Google's cache is the snapshot that we took of the page as we crawled the web.

The page may have changed since that time. Click here for the [current page](#) without highlighting.

This cached page may reference images which are no longer available. Click here for the [cached text](#) only.

To link to or bookmark this page, use the following url: <http://www.google.com/search?q=cache:wppMFsfJQooJ:www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html+atm+p53+ataxia&hl=en&gl=us&ct=clnk&cd=4>

<http://www.google.com/search?q=cache:wppMFsfJQooJ:www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html+atm+p53+ataxia&hl=en&gl=us&ct=clnk&cd=4>

*Google is neither affiliated with the authors of this page nor responsible for its content.*

These search terms have been highlighted: **atm p53 ataxia**

## Atlas of Genetics and Cytogenetics in Oncology and Haematology

[Home](#) [Genes](#) [Leukemias](#) [Solid Tumours](#) [Cancer-Prone](#) [Deep Insight](#) [Portal](#) [Teaching](#)

[X](#) [Y](#) [1](#) [2](#) [3](#) [4](#) [5](#) [6](#) [7](#) [8](#) [9](#) [10](#) [11](#) [12](#) [13](#) [14](#) [15](#) [16](#) [17](#) [18](#) [19](#) [20](#) [21](#) [22](#) [NA](#)

# Ataxia telangiectasia

## Identity

<b>Note</b>	see also, in Deep Insight section: <a href="#">Ataxia-Telangiectasia and variants</a>
<b>Other names</b>	Louis-Bar syndrome
<b>Inheritance</b>	autosomal recessive; frequency is about 1 to 2.5/105 newborns; heterozygotes are estimated to be 1% of the general population; founder effect are found in some isolated population

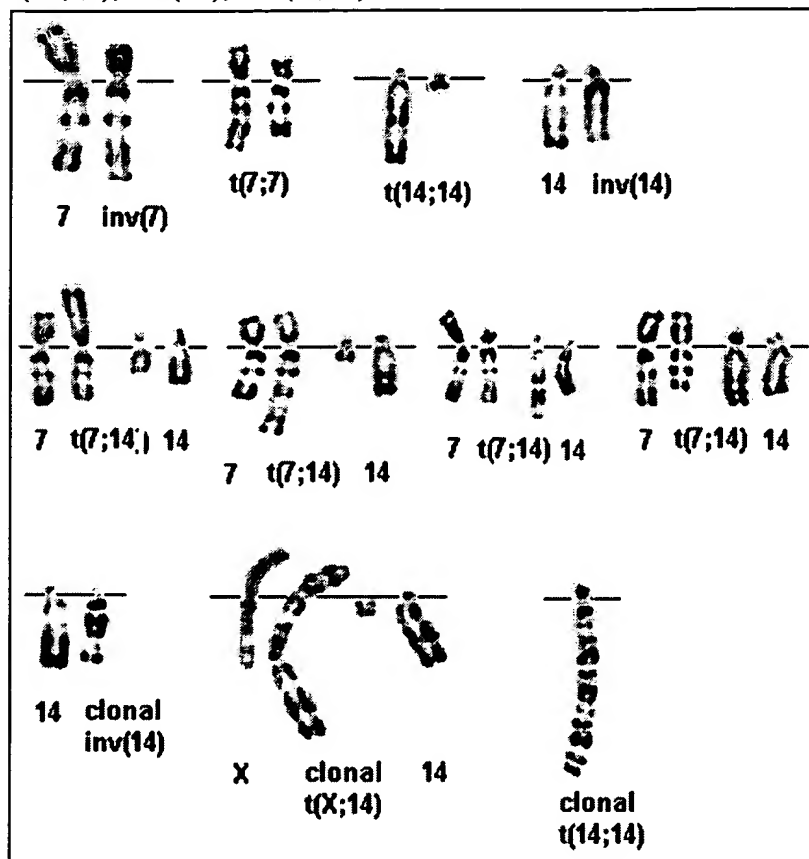
## Clinics

<b>Note</b>	<b>ataxia</b> telangiectasia is a chromosome instability syndrome with cerebellar degeneration, immunodeficiency, and an increased risk of cancers; A-T cells are defective in recognizing double-strand DNA damage to signal for repair
<b>Phenotype and clinics</b>	<ul style="list-style-type: none"> <li>onset of the disease is often noted during the second year of life: there is progressive cerebellar <b>ataxia</b> (initially truncal, with further peripheral extension); <b>ataxia</b> is a constant feature in this disease; oculomotor apraxia, dysarthria, and dystonia; leading to muscular atrophy</li> <li>telangiectasia: facial region exposed to sunlight, and eyes (conjunctiva)</li> <li>combined immunodeficiency (in 70 %): thymus hypoplasia, and IgG2 and 4, IgA, IgE deficiency</li> <li>other features: growth retardation; hypogonadism; occasionally diabetes mellitus</li> </ul>
<b>Neoplastic risk</b>	<ul style="list-style-type: none"> <li>risk of cancers is X 100, consisting mainly of T- cell malignancies (a 70-fold and 250-fold increased risks of leukemia and lymphoma respectively) and B-cell malignancies, but not myeloid leukemia; carcinomas of the skin, ovary, breast, and stomach have also been described</li> <li>cancer treatment is complicated by radiation- and chemo-sensitivity</li> </ul>
<b>Evolution</b>	progressive cerebellar degeneration: patients are usually in a wheelchair by the age of ten
<b>Prognosis</b>	<ul style="list-style-type: none"> <li>respiratory infection is the common cause of death, with cancer being the second most common.</li> <li>survival is often into fourth decade today where optimal medical care is available</li> </ul>

## Cytogenetics

### Inborn conditions

- spontaneous chromatid/chromosome breaks, triradials, quadriradials (less prominent phenomenon than in **Fanconi anaemia**); telomeric associations
- the best diagnosis test is on the (pathognomonic) highly elevated level (10% of mitoses) of inv(7) (p14q35), t(14;14)(q11;q32), and other non clonal stable chromosome rearrangements involving 2p12, 7p14, 7q35, 14q11, 14q32, and 22q11 (illegitimate recombinations between immunoglobulin superfamily genes Ig and TCR); normal level of those rearrangements are: 1/500 (inv(14)), 1/200 (t(7;14)), 1/10 000 (inv(7))
- clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14)



Sporadic (rows 1 and 2) and clonal (row 3) rearrangements in ataxia telangiectasia (R- banding). Row 1, from left to right: inv(7)(p14q35), t(7;7)(p14;q35), t(14;14)(q11;q32), inv(14)(q11;q32); Row 2, from left to right: t(7;14)(p14;q11), t(7;14)(q35;q11), t(7;14)(p14;q32), t(7;14)(q35;q32); Row 3, from left to right: inv(14)(q11;q32), t(X;14)(q28;q11) (note the late replicating X on the left), t(14;14)(q11;q32) - Courtesy Alain Aurias (modified figure reprinted from Médecine/Sciences 1986; 2: 298-303., by permission of the publisher Masson).

### Cytogenetics of cancer

clonal rearrangements in T-cell ALL and T-PLL (prolymphocytic leukaemia) in AT patients are complex, with the frequent involvement of t(14;14)(q11;q32)(q11;q32), or t(X;14)(q28;q11), implicating the genes **TCL1** or **MTCP1** respectively, as is found in T-PLL in non-AT patients

### Other findings

#### Note

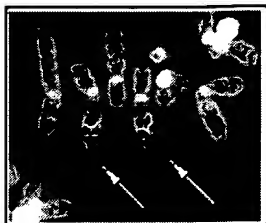
- high sensitivity to ionizing radiations and to radiomimetic drugs (diagnostic may in part be based on the hypersensitivity of AT lymphocytes to killing by gamma irradiation); cell irradiation does not inhibit S phase (DNA synthesis): this is quite pathognomonic of AT, and shows that G1 checkpoint is deficient; there is a lack of **P53**, **GADD45** and **P21** induction, and a fall in radiation-induced apoptosis; **P53** phosphorylation at ser15 is deficient
- lengthening of the cell cycle
- difficult to grow cells with phytohemagglutinin: karyotypes should be performed with interleukine 2 in 4 days cultures
- other: increased level of serum alpha-fetoprotein

## Genes involved and Proteins

**Gene Name** **ATM (Ataxia telangiectasia mutated)** is responsible for the vast majority of A -T cases.

**Location** 11q22-q23.1

**DNA/RNA**



**ATM** (11q22.3) in normal cells: PAC 891P24 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are wellcome: contact M Rocchi

**Description** 66 exons spanning 184 kb of genomic DNA

### Protein

**Description** 3056 amino acids; 350 kDa; contains a PI 3-kinase-like domain

**Localisation** mostly in the nucleus in replicating cells, cytoplasm in differentiating cells

**Function** mediates cell cycle arrest in response to ionizing radiation through the phosphorylation of targets including **p53**, **cAbl**, **BRCA1**, **H2AX**, **IkB-alpha** and **chk1**

### Mutations

**Germinal** various types of mutations, dispersed throughout the gene, and therefore most patients are compound heterozygotes; however, most mutations appear to inactivate the **ATM** protein by truncation, large deletions, or annulation of initiation or termination. Missense mutations have been described in breast cancer patients, but do not seem to contribute to **ataxia-telangiectasia**.

### To be noted

- heterozygote cancer risk: the relative risk of breast cancer in A-T heterozygote women has been estimated through epidemiological studies to be 3.9 (CI 2.1-7.1), and through haplotype analysis to be 3.32 (CI 1.75-6.38); since the A-T heterozygote frequency is about 1 %, 2-4 % of breast cancer cases may be due to **ATM** heterozygosity; the risk of other types of cancer in A-T heterozygotes is low
- the A-T variant Nijmegen breakage syndrome does not involve the same gene.

### External links

GeneCards **ATM**

GDB **ATM**

OMIM 208900

Orphanet **Ataxia telangiectasia**

HGMD 593364

**Other database** **Ataxia-Telangiectasia - GeneClinics**

**Association** The A-T Children's Project



Association [Ataxia-Telangiectasia Mutation Database](#)

Registry <http://www.vmmc.org/vmrc/atm.htm>

## Bibliography

### **New data on clonal anomalies of chromosome 14 in ataxia telangiectasia: tct(14;14) and inv(14).**

Aurias A, Croquette MF, Nuyts JP, Griscelli C, Dutrillaux B

Hum Genet 1986; 72(1): 22-24

Medline [86110162](#)

### **Probable involvement of immunoglobulin superfamily genes in most recurrent chromosomal rearrangements from ataxia telangiectasia.**

Aurias A, Dutrillaux B

Hum Genet 1986; 72(3): 210-214

Medline [86166490](#)

### **Ataxia-telangiectasia: an inherited disorder of ionizing-radiation sensitivity in man. Progress in the elucidation of the underlying biochemical defect**

McKinnon PJ

Hum Genet 1987; 75(3): 197-208

Medline [87164160](#)

### **Molecular characterization of different ataxia telangiectasia T-cell clones. I. A common breakpoint at the 14q11.2 band splits the T-cell receptor alpha-chain gene.**

Stern MH, Zhang FR, Griscelli C, Thomas G, Aurias A

Hum Genet 1988; 78(1): 33-36

Medline [88113639](#)

### **Molecular characterization of ataxia telangiectasia T cell clones. III. Mapping the 14q32.1 distal breakpoint.**

Stern MH, Zhang FR, Thomas G, Griscelli C, Aurias A

Hum Genet 1988; 81(1): 18-22

Medline [89065718](#)

### **Incidence of cancer in 161 families affected by ataxia-telangiectasia.**

Swift M, Morrell D, Massey RB, Chase CL

N Engl J Med 1991; 325(26): 1831-1836

Medline [92072632](#)

### **The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species.**

Savitsky K, Sfez S, Tagle DA, Ziv Y, Sartiel A, Collins FS, Shiloh Y, Rotman G

Hum Mol Genet 1995; 4(11): 2025-2032

Medline [96154672](#)

### **Atm-deficient mice: a paradigm of ataxia telangiectasia.**

Barlow C, Hirotsumi S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, Wynshaw-Boris A

Cell 1996; 86(1): 159-171

Medline [96291408](#)

### **Leukemia and lymphoma in ataxia telangiectasia.**

Taylor AM, Metcalfe JA, Thick J, Mak YF

Blood 1996; 87(2): 423-438

Medline [96141061](#)

**Atm selectively regulates distinct p53-dependent cell-cycle checkpoint and apoptotic pathways.**

Barlow C, Brown KD, Deng CX, Tagle DA, Wynshaw-Boris A

Nat Genet 1997; 17(4): 453-456

Medline [98061096](#)

**Ataxia-telangiectasia locus: sequence analysis of 184 kb of human genomic DNA containing the entire ATM gene.**

Platzer M, Rotman G, Bauer D, Uziel T, Savitsky K, Bar-Shira A, Gilad S, Shiloh Y, Rosenthal A

Genome Res 1997; 7(6): 592-605

Medline [97343327](#)

**Cell-cycle signaling: Atm displays its many talents.**

Westphal CH

Curr Biol 1997; 7(12): R789-792

Medline [98044309](#)

**ATM-heterozygous germline mutations contribute to breast cancer-susceptibility.**

Broeks A, Urbanus JH, Floore AN, Dahler EC, Klijn JG, Rutgers EJ, Devilee P, Russell NS, van Leeuwen FE.

Am J Hum Genet 2000; 66(2): 494-500.

Medline [10677309](#)

**ATM phosphorylates histone H2AX in response to DNA double-strand breaks.**

Burma S, Chen BP, Murphy M, Kurimasa A, Chen DJ.

J Biol Chem 2001; 276(45): 42462-42467.

Medline [11571274](#)

**REVIEW articles**

*automatic search in PubMed*

**Last year publications**

*automatic search in PubMed*

**Contributor(s)**

<b>Written</b>	04-1998	Jean Loup Huret
<b>Updated</b>	10-1999	Nancy Uhrhammer, Jacques-Olivier Bay and Richard A Gatti
<b>Updated</b>	10-2002	Nancy Uhrhammer, Jacques-Olivier Bay and Richard A Gatti

**Citation**

*This paper should be referenced as such :*

**Huret JL . Ataxia telangiectasia.** Atlas Genet Cytogenet Oncol Haematol. April 1998 .

URL : <http://www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html>

**Uhrhammer N, Bay JO, Gatti RA . Ataxia telangiectasia.** Atlas Genet Cytogenet Oncol Haematol. October 1999 .

URL : <http://www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html>

**Uhrhammer N, Bay JO, Gatti RA . Ataxia telangiectasia.** Atlas Genet Cytogenet Oncol Haematol. October 2002 .

URL : <http://www.infobiogen.fr/services/chromcancer/Kprones/ataxia.html>

For comments and suggestions or **contributions**, please contact us  
[j.l.huret@chu-poitiers.fr](mailto:j.l.huret@chu-poitiers.fr).

---

This is Google's cache of [http://www.sigmaaldrich.com/Area\\_of\\_Interest/Life\\_Science/Cell\\_Signaling/Key\\_Resources/Pathway\\_Slides\\_Charts/](http://www.sigmaaldrich.com/Area_of_Interest/Life_Science/Cell_Signaling/Key_Resources/Pathway_Slides_Charts/)  
Jun 1, 2006 15:46:44 GMT.

Google's cache is the snapshot that we took of the page as we crawled the web.

The page may have changed since that time. Click here for the current page without highlighting.

This cached page may reference images which are no longer available. Click here for the cached text only.

To link to or bookmark this page, use the following url: [http://www.google.com/search?](http://www.google.com/search?q=cache:W4FGrdCZJGsJ:www.sigmaaldrich.com/Area_of_Interest/Life_Science/Cell_Signaling/Key_Resources/Pathway_Slides_Charts/)

[q=cache:W4FGrdCZJGsJ:www.sigmaaldrich.com/Area\\_of\\_Interest/Life\\_Science/Cell\\_Signaling/Key\\_Resources/Pathway\\_Slides\\_Charts/](http://www.google.com/search?q=cache:W4FGrdCZJGsJ:www.sigmaaldrich.com/Area_of_Interest/Life_Science/Cell_Signaling/Key_Resources/Pathway_Slides_Charts/)

Google is neither affiliated with the authors of this page nor responsible for its content.

These search terms have been highlighted: atm p53 ataxia

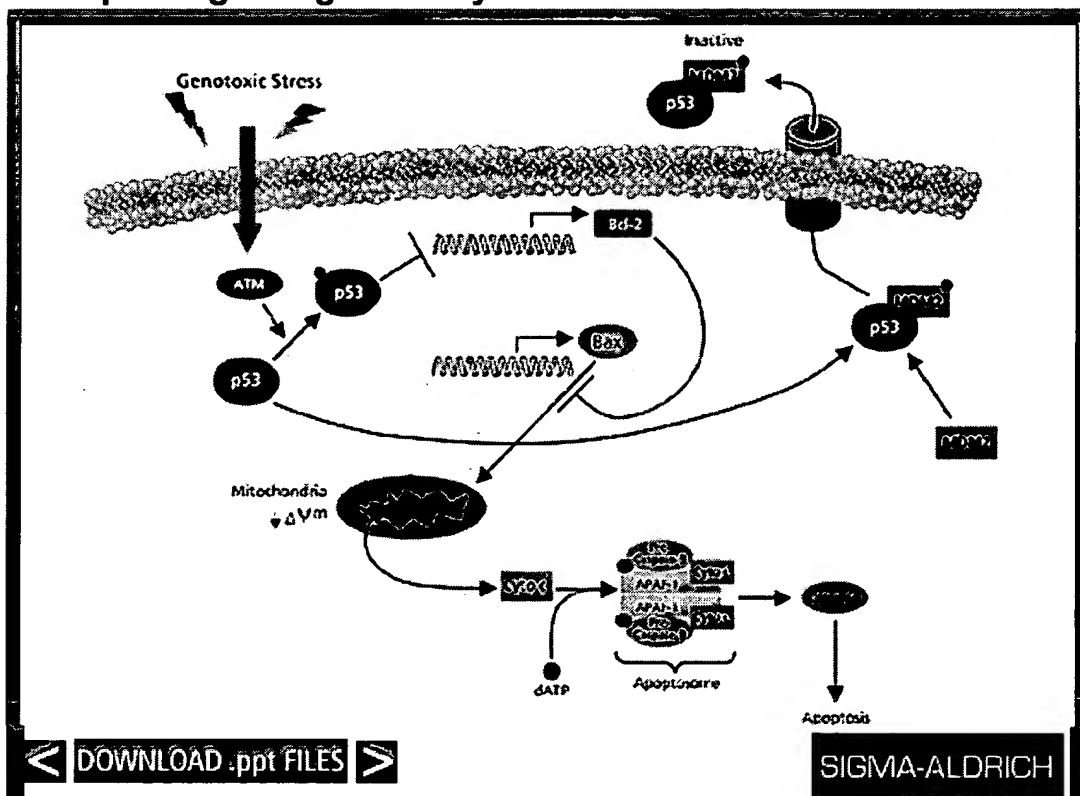


Register for additional site benefits. | [Login](#) | [Your Profile](#) | [Order Center](#) | [Search](#) | [Support](#) | [Help](#)

#### Life Science

- + Antibody Explorer
- + Automation
- + Cancer Research
- + Cell Culture
- Cell Signaling
  - + Product Lines
  - + Product Highlights
  - + New Literature
  - + Celltransmissions News
- Key Resources
  - Cell Biology Assays
  - New Products
  - Pathway Slides & Charts
  - Pharm. Action Table
- Custom Synthesis
- Drug Discovery
- + Functional Genomics and RNAi
- + Metabolomics
- + Molecular Biology
- + Nutrition Research
- + Obesity Research
- + Plant Biotechnology
- + Proteomics and Protein Expr.
- Stable Isotopes
- + Life Science Quarterly
- PathFinder

## ATM/p53 Signaling Pathway



Slides

[Click Here For Products  
Related To Slide](#)

## ATM/p53 Signaling Pathway

The ataxia telangiectasia-mutated gene (ATM) encodes a protein kinase that acts as a tumor suppressor. ATM activation, via IR damage to DNA, stimulates DNA repair and blocks cell cycle progression. One mechanism through which this occurs is ATM dependent phosphorylation of p53. p53 can cause growth arrest of the cell at a checkpoint to allow for DNA damage repair or can cause the cell to undergo apoptosis if the damage

cannot be repaired. The critical role of **p53** is evident by the fact that it is mutated in over 50% of all human cancers.

[Back to Top](#)

Use of this web site constitutes your acceptance of the [Site Use Terms](#)

[privacy](#) | [terms and conditions](#) | [Business Development](#)

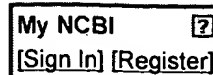
---

© 2006 Sigma-Aldrich Co. *Reproduction forbidden without permission.*

*Sigma-Aldrich brand products are sold exclusively through Sigma-Aldrich, Inc. Best viewed in IE6 or higher*



A service of the National Library of Medicine  
and the National Institutes of Health



All Databases

PubMed

Nucleotide

Protein

Genome

Structure

OMIM

PMC

Journals

Books

Search  for

Limits

Preview/Index

History

Clipboard

Details

Display  Show  Sort by  Send to

All: 1 Review: 0

About Entrez

Text Version

Entrez PubMed

Overview

Help | FAQ

Tutorials

New/Noteworthy

E-Utilities

PubMed Services

Journals Database

MeSH Database

Single Citation Matcher

Batch Citation Matcher

Clinical Queries

Special Queries

LinkOut

My NCBI

Related Resources

Order Documents

NLM Mobile

NLM Catalog

NLM Gateway

TOXNET

Consumer Health

Clinical Alerts

ClinicalTrials.gov

PubMed Central

☐ 1: Cell. 1996 Jul 12;86(1):159-71.

Related Articles, Links

**Cell Press**

### Atm-deficient mice: a paradigm of ataxia telangiectasia.

Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, Wynshaw-Boris A.

Laboratory of Genetic Disease Research, National Center for Human Genome Research, National Institutes of Health, Bethesda, Maryland 20892, USA.

A murine model of ataxia telangiectasia was created by disrupting the Atm locus via gene targeting. Mice homozygous for the disrupted Atm allele displayed growth retardation, neurologic dysfunction, male and female infertility secondary to the absence of mature gametes, defects in T lymphocyte maturation, and extreme sensitivity to gamma-irradiation. The majority of animals developed malignant thymic lymphomas between 2 and 4 months of age. Several chromosomal anomalies were detected in one of these tumors. Fibroblasts from these mice grew slowly and exhibited abnormal radiation-induced G1 checkpoint function. Atm-disrupted mice recapitulate the ataxia telangiectasia phenotype in humans, providing a mammalian model in which to study the pathophysiology of this pleiotropic disorder.

#### MeSH Terms:

- Animals
- Ataxia Telangiectasia/genetics
- Ataxia Telangiectasia/immunology
- Ataxia Telangiectasia/physiopathology\*
- Cell Cycle/genetics
- Cell Cycle Proteins
- Cell Division/genetics
- DNA-Binding Proteins
- Disease Models, Animal
- Dose-Response Relationship, Radiation
- Female
- Fibroblasts/cytology
- Fibroblasts/physiology
- Germ Cells/cytology
- Germ Cells/physiology
- Leucine Zippers/genetics
- Lymphoma/genetics
- Male
- Mice

- [Mice, Mutant Strains](#)
- [Mutation/immunology](#)
- [Mutation/physiology](#)
- [Mutation/radiation effects](#)
- [Neurologic Examination](#)
- [Protein-Serine-Threonine Kinases\\*](#)
- [Proteins/genetics\\*](#)
- [Research Support, U.S. Gov't, P.H.S.](#)
- [Thymus Neoplasms/genetics](#)
- [Tumor Suppressor Proteins](#)

## Substances:

- [Cell Cycle Proteins](#)
- [DNA-Binding Proteins](#)
- [Proteins](#)
- [Tumor Suppressor Proteins](#)
- [Protein-Serine-Threonine Kinases](#)
- [ataxia telangiectasia mutated protein](#)

PMID: 8689683 [PubMed - indexed for MEDLINE]

---

Display  Show  Sort by  Send to

[Write to the Help Desk](#)  
[NCBI](#) | [NLM](#) | [NIH](#)  
[Department of Health & Human Services](#)  
[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

May 30 2006 06:41:35